

REVIEW

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Oral surgery in patients under antithrombotic therapy. Narrative review.

Abstract: Population aging and the increasing rates of cardiovascular diseases have raised the number of patients receiving antithrombotic therapy in elective or emergency dental care, including surgical procedures. The aim of this article is to review the evidence and clinical guidelines for management of patients on antithrombotic therapy published in the past five years. The American Antithrombotic Therapy Guideline - 2012 - generally recommends not to suspend antiplatelet or anticoagulant treatment in dental procedures since they are considered to have low bleeding risk and easy resolution. In the dental field, there is ample published evidence regarding oral surgical procedure management, especially by maxillofacial surgeons, showing a low number of complications associated with extractions or other minor oral surgical procedures without suspending antithrombotic drugs and only taking some minimum safeguards, such as healing by first intention or the use of some local hemostatic agents. In general, patients under chronic antithrombotic therapy should keep their medication when undergoing low and medium complexity dental procedures, since complications are minor and easy to handle. Due to interactions between them, particular care should be taken with patients using more than one drug.

Keywords: Antithrombotic, coagulation, exodontia, oral surgery, hemorrhage, aspirin.

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INTRODUCTION.

Population aging and the increasing prevalence of chronic diseases, especially the cardiovascular ones, make cardiac events the main cause of death in developed countries and this is also happening in Chile¹. Although there are several ways to intervene and prevent cardiovascular diseases (CVD), the pharmacological treatment is the most important. Prescribing antithrombotic drugs is currently the most used strategy to prevent the development of a major cardiac event^{2,3}.

Given that, it is becoming more and more frequent to find patients with CVD treated with antithrombotic therapy in the dental office². This makes it necessary for the dentist to consider certain handling guidelines to avoid triggering a cardiac event and allow relevant and efficient care for these patients, especially in emergency situations involving routine and low complexity surgical procedures.

The objective of this article is to review the evidence and international clinical guidelines with regard to the management of dental patients treated with antithrombotic therapy published in the last 5 years. This is intended to generate recommendations for the national context according to today's patients' risk level.

Antithrombotic drugs.

Currently, in Chile, the most commonly used antithrombotic drugs are acetylsalicylic acid (aspirin), acenocoumarol (Neosintron), warfarin (Coumadin) and clopidogrel⁴. Antithrombotics for ambulatory use can be classified into 2 groups:

Antiplatelet: they inhibit platelet activation pathways. The most commonly used are acetylsalicylic acid (aspirin) and clopidogrel. Acetylsalicylic acid is a COX - 1inhibitor. It affects thromboxane A_2 synthesis to achieve a persistent and almost complete suppression of platelet COX (COX-1) for more than 24 hours. The usual dose ranges from 85 to 325mg/day⁵.

Clopidogrel has an active metabolite that selectively inhibits the binding of the adenosine diphosphate to its platelet P2Y12 receptor and the subsequent ADP mediated activation of the GPIlb/Illa complex, thus inhibiting platelet aggregation. The usual dose is 75mg/day⁵.

These drugs are mostly used in prophylaxis or treatment of arterial thrombosis in patients with cardiovascular disease, particularly in coronary heart disease⁵.

Anticoagulants: The most current usage corresponds to vitamin K antagonists (VKA), such as warfarin and acenocoumarol (Neosintron).

Warfarin acts on vitamin K-dependent clotting factors (II, VII, IX and X), inhibiting primarily extrinsic and common pathways of coagulation⁵. Doses must be adjusted on the basis of the patient's INR and the condition treated. There are medications that affect its power; the R-warfarin is metabolized by the CYP1A2 and CYP 3A4 and is inhibited by quinolones, macrolides, as well as metronidazole and fluconazole⁶. Its main indication is for prophylaxis and/or treatment of venous thrombosis, pulmonary embolism, thromboembolic complications associated with atrial fibrillation, heart valve replacement and recurrence of myocardial infarction or cerebrovascular accident⁶.

Acenocoumarol (Neosintron) has an anticoagulant effect due to the inhibition of the epoxide reductase enzyme, interfering in the gamma-carboxylation of glutamate residues in factors II, V, VII and IX, in addition to inhibiting carboxylation of protein C and S⁷. Substances such as omeprazole may enhance the effect of acenocoumarol⁸. Its indication is similar to warfarin and no significant difference was found between them⁷.

CLINICAL GUIDELINES FOR ANTITHROM-BOTIC THERAPY.

Regarding preoperative management of these patients, there are rules set forth in the clinical guidelines for antithrombotic therapy, published in CHEST 2012⁹.

The main indications are the following:

1. Perioperative management of users of VKA: In patients who require a minor dental procedure, it is suggested to continue with the AVK associated with the co-administration of an oral pro-hemostatic agent or suspend AVK two or three days before the procedure (evidence grade: 2c).

2. For patients undergoing a minor dental procedure who are receiving aspirin for secondary prevention of cardiovascular disease, it is suggested to continue its administration rather than suspending it 7 to 10 days prior to the procedure (evidence grade: 2C).

2.1 In patients with moderate to high risk of cardiovascular events and who are receiving aspirin, it is suggested to continue rather than suspending it 7 to 10 days before surgery (evidence grade: 2C). In patients with low risk of cardiovascular events who are receiving aspirin, it is suggested to suspend it 7 to 10 days before the procedure (evidence grade: 2C).

These recommendations are essentially the same as those on the preoperative management of chronic antithrombotic therapy made in the revision published in BLOOD in 2012¹⁰. Dental procedures are considered to have a low bleeding risk and it is recommended to continue using AVK together with the concomitant administration of a pro-hemostatic agent (for example, an antifibrinolytic agent, such as tranexamic acid or aminocaproic acid used as a mouth rinse before and after the procedure), or interrupt VKA only 2-3 days before. This results in an INR which is slightly subtherapeutic at the time of the procedure. Regarding antiplatelet therapy, the suggestion is not to stop it. Other recommendations which are closer to local reality (Cuba) show that, in moderate bleeding risk surgery (cardiac surgery, orthopaedic, major abdominal, otorhinolaryngological and urological), if there is a high thrombosis risk, aspirin should be kept, Clopidogrel should be suspended between 3 and 5 days prior to the surgical procedure. If the thrombotic risk is intermediate, aspirin should be used between 10 and 14 days prior to the surgical procedure¹¹.

In general, all guidelines indicate treatment with oral anticoagulants for surgical oral procedures should not be stopped since bleeding during the intra-operative and postoperative period is easy to handle and resolve, not so the consequence of stopping therapy.

EVIDENCE OF DENTAL MANAGEMENT.

In the dental field, several research papers and revisions with different level of evidence, patient type and antithrombotic therapy have recently been published, but, in general, they reaffirm what is stated in cardiovascular and hematologic clinical guidelines.

Recently, Girotra et al.¹² analyzed the bleeding risk in patients with prolonged antiplatelet drugs, specifically aspirin and clopidogrel, as well as the combination of these. The subjects were compared with patients who were not taking them and only minor oral surgery procedures which included multiple extractions, surgical extractions, lifting flaps, alveoloplasties and biopsies were performed. With consent from the patient, the patient's physician or cardiologist and the dentist, none of those under antiplatelet therapy suspended medicines for the surgery, which were carried out in an ambulatory setting and with standard surgical protocols. A higher prevalence of prolonged bleeding was found in patients under dual therapy (aspirin and clopidogrel), but the correlation between both variables was poor. Depending on the type of procedure, patients with antiplatelet drugs showed a more prolonged bleeding when they were subjected to surgical extractions, lifting of flaps and biopsies, but the difference was not statistically significant. Notwithstanding, all patients with a

prolonged bleeding were successfully managed with simple local hemostatic measures such as pressure, wound suturing, gel foam, electrocoagulation or the topical use of thrombin, tranexamic acid or 1% feracrylum solution. Feracrylum is an effective and safe topical hemostatic agent to minimize significantly diffuse capillary exudation and superficial hemorrhage, thus reducing intraoperative blood loss, postoperative hematoma, edema of the wound and postoperative complications¹³. The authors conclude that only patients under dual therapy have an increased risk of prolonged bleeding so they should always be sutured. Also, bleeding is controllable with local measures; therefore, it is not necessary to suspend drugs due to increased thrombogenic risk.

On the other hand, Broekema *et al.*¹⁴ analyzed the bleeding risk in patients on anticoagulants (INR 1.8 to 3.5) compared with patients on antiplatelet therapy and a control group that did not take this type of medications. The objective of the study was to evaluate the effectiveness of the ACT protocol, which indicates the use of mouthwash with tranexamic acid (4 times per 5 days) in patients under anticoagulant therapy. Patients on anticoagulants showed a greater prevalence of mild bleeding, but it was not statistically significant. The authors concluded on the proper effectiveness of the protocol, but it is necessary to investigate in elderly population.

Svensson *et al.*¹⁵ analyzed the effectiveness of using hemostatic or collagen sponge and suture and tranexamic acid to prevent increased bleeding in patients using warfarin (INR \leq 3.5). Out of 124, five patients had postoperative bleeding, all of them due to extraction in the jaw molar area and 2 associated with the concomitant use of aspirin and warfarin. These 5 patients were managed with local measures and none required hospitalization. The authors conclude that there is a low bleeding risk in patients who take warfarin and the utility of minimum coagulation measures. However, clinical trials are needed to determine the role of these measures for managing patients treated with antithrombotic therapy.

Regarding management of patients receiving warfarin

sodium, a review revealed little or no risk of significant hemorrhage in patients with a TP 1.5 to 2 times higher than normal after surgical procedures. Also, it reported that there is little risk of hemorrhagic complications as long as the TP is up to 2.5 times the normal value and that the risk of complications is greater when the anticoagulant therapy is stopped¹⁶.

Ripolles-Ramon *et al.*¹⁷ investigated the effect of the tranexamic acid gel in post extraction healing in patients undergoing anticoagulant therapy (acenocoumarol) and a control group. The results indicate that the use of the gel reduces healing time in patients under anticoagulant drugs, but not in the control group and patients did not report episodes of excessive bleeding. The authors conclude about the potential usefulness of this new presentation form of the tranexamic acid gel.

Okamoto *et al.*¹⁸ compared the effect of the hemostatic sponge gel, blue-violet LED and the combination of both in the prevention of post-extraction bleeding in patients under warfarin, not control groups were included for the treatment or type of patient. The results show a synergistic effect in the use of LED and the sponge. The authors conclude about the utility of this new method, described as easy to use, but that further research is needed in this regard, including dental extractions and other types of dental procedures.

In addition to the most commonly used antithrombotic medication, new drugs have been developed and recently approved by the FDA. One of them is dabigatran, a direct thrombin inhibitor¹⁹. Romond *et al.*²⁰ describe handling of a patient under this medication whom had 8 extractions, alveoloplasty and tuberosity reduction. In this case and with medical consent, dabigatran was suspended the night before the procedure and restarted the day after. There were no immediate postoperative complications nor in a 7-month follow-up period. Unlike management described in the literature, the authors support the suspension of dabigatran in accordance with the recommendations by Van Ryn *et al.*²¹, as well as the fact of the extent of the procedure and the absence of an agent to reverse the effect of dabigatran. However, the authors agree that in minor procedures (1 to 3 extractions), stopping the medication would not be indicated. Given the recent incorporation of dabigatran, further research is needed regarding its effect in patients undergoing dental procedures.

In addition to the drugs taken by patients with chronic diseases, possible interactions with those that are indicated by the dentist should be considered. For example, Goodchild and Donaldson²² describe the interaction between warfarin and amoxicillin in a patient who was subjected to multiple extractions. In this case, INR increase from 2.0 to 5.8 was seen with the use of amoxicillin (which is a range for ASA IV patients). Therefore, additional measures were required for up to 1 week after the procedure. This interaction with warfarin adds to the already reported for the use of NSAIDS, which must be used with caution, after oral surgeries²³.

Most of the evidence indicates that surgical procedures such as tooth extractions or limited periodontal surgery may be executed without modification of INR values except in extreme circumstances. Prolonged postoperative hemorrhage occurs rarely with INR in range of 1.0 to 3.0, however higher levels would be associated with mild and moderate localized bleeding¹⁶.

A recent systematic review about the bleeding risk in patients treated with antiplatelet therapy who were subjected to dental procedures^{24,25} concludes in a similar manner as the previously described: although patients using these medications have an increased bleeding, it is not clinically relevant and can be easily handled with local measures, paying special attention to those patients using more than one medication. Given the above, it is recommended not to alter or suspend antithrombotic therapy and highlight the need to continue researching this topic.

A practical and simplified vision is given by Wahl²⁶ when noting "bleed or die" because the evidence is broad in pointing out a low bleeding risk in these patients, which are easily controllable and that the suspension of these drugs involve pondering about exposing patients to a remote bleeding risk with non-fatal consequences versus

exposing them to a small risk, but fatal due to a thromboembolic complication.

Current evidence suggests that, in most cases, the risk does not have a significant clinical impact. Even more, in many situations, stopping medication, and/or performing bridge therapy does not provide adequate protection, but increases embolic or thrombotic phenomena risk and may even be associated with increased hemorrhagic phenomena risk. Therefore, it is essential to carry out an individualized assessment to define the bleeding risk associated with each surgical procedure and compare it with thrombotic risk, and embolic cardiovascular mortality associated with the suspension of these medications. Only in this way, it will provide the best therapeutic option for each patient²⁵.

DISCUSSION.

Patients treated with antithrombotic therapy do not represent a significant percentage of the general population and therefore those who receive dental treatment, in Spain are only 1.89%²⁷. However, the underlying pathologies (CVD) imply the need for special clinical management. Additionally, it should not be ignored that the increase in the risk factors for CVD² will lead to a greater presence of these patients in dental consultations during the coming years. They must be stabilized to perform minor oral surgery, which are generally elective procedures. It is necessary to clarify that the reference to oral surgery in the reviewed literature includes simple and flap extractions, osteotomies, cystectomies, alveoloplasties and other procedures of minor or medium complexity.

While there are no precise numbers as to how the dentists manage these patients in Chile, an investigation in Dutch maxillofacial surgeons found that there was an overestimation of the bleeding risk that led to an inadequate management in view of the current evidence, materialized in risky behaviors such as the suspension of the medication for the realization of invasive oral procedures²⁸.

Considering this, it is not uncommon to find in the Chilean context a poorly focused and excessive caution for hemorrhages associated with dental procedures. Many patients are suspended from their antithrombotic medication mainly to conduct low risk and short duration oral surgeries that are not justified.

In patients with low thrombotic risk, who usually take aspirin, the suspension should take 7 days to decrease the antiaggregation effect. In the case of patients recieving more than one antithrombotic medication, the bleeding risk increases, but it is precisely these patients who have an increased thrombotic risk and the suspension of the medication exposes them to an event of serious consequences, while excessive bleeding can be prevented or controlled in a simple way without major complications. Thus, it is always necessary to assess what is more dangerous.

On the other hand, there may be unnecessary referrals for the physician to "authorize" a procedure. This becomes important in those patients who have acute and intense pain and/or an infection in progress. In these cases, an oral surgery can be performed with a low bleeding risk, prior evaluation of the patient's medical history. Unless there is some pathology or concomitant medication of relevance for the dental procedure (usually simple extractions), this should not be postponed because of the mere presence of an antithrombotic medication. It is important to consider that leaving an odontogenic infection without treatment in its initial stages will generally lead to a process of greater seriousness that will require hospitalization, unnecessarily exposing the patient and generating higher health care costs.

Although much of the recent literature mentions procedures for controlling bleeding require special implements¹²⁻²¹, which are not usually available in most of the Chilean hospital facilities, there are still other simple procedures applied locally in the surgical area. These include initial hemostasis control before dispatching the patient, follow-up appointments in the following days, pressure bleeding area or simple wound suturing and closure by first intention. In this sense, the possibility to manage these patients in a simple manner, without interrupting their antithrombotic therapy or generating unnecessary referrals and inter-consultations, is reaffirmed.

In spite of all of the above, it is always necessary to consider that patients under antithrombotic therapy often present a series of concomitant pathologies and take multiple medications that could alter the decision to perform a specific dental procedure. In these cases, medical inter-consultation is necessary to clear up doubts and reduce risks.

CONCLUSION.

In general terms, patients undergoing chronic an-

Cirugía bucal en pacientes con terapia antitrombótica. Revisión narrativa.

Resumen: El envejecimiento poblacional y el aumento patologías cardiovasculares ha aumentado la cantidad de pacientes bajo terapia antitrombótica que reciben atención dental electiva o de urgencia, incluidos los procedimientos quirúrgico. El objetivo de este artículo es revisar la evidencia y las guías clínicas publicadas en los últimos 5 años respecto al manejo odontológico de pacientes bajo terapia antitrombótica. La guía clínica americana de terapia antitrombótica del año 2012 recomienda en general no suspender la terapia antiplaquetaria ni anticoagulante, en los procedimientos dentales ya que son considerados como de bajo riesgo de sangrado y de fácil resolución. En el área odontológica existe amplia evidencia publicada respecto al manejo de procedimientithrombotic therapy should keep their medicines when they are subjected to dental procedures. Possible complications are minor and their resolution is easy, while their suspension can lead to complications that could be fatal. Special attention must be paid to patients using more than one medication, concomitant disorders, who use the latest generation anticoagulant drugs and the interactions with drugs prescribed during dental treatment. Only in these cases, medical inter-consultation may be necessary.

tos quirúrgicos bucales, especialmente por cirujanos maxilofaciales, que ha demostrado la baja cantidad de complicaciones asociadas a exodoncias u otras cirugías menores de la cavidad bucal; sin la necesidad de suspender los medicamentos antitrombóticos y tomando algunos resguardos mínimos como la cicatrización por primera intención o el uso de algunos agentes hemostáticos locales. En términos generales los pacientes bajo terapia antitrombótica crónica deben mantener sus medicamentos cuando son sometidos a procedimientos dentales de baja y mediana complejidad, ya que las complicaciones son menores y de sencillo manejo. Se debe poner especial atención en pacientes con más de un medicamento, por las interacciones entre ellos.

Palabras clave: Antitrombótico, Coagulación, Exodoncia, Cirugía bucal, Hemorragia, Aspirina.

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